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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/512,568	02/24/2000	Mich B. Hein	TSRI-184.2Con3	5810

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EXAMINER	
COLLINS, CYNTHIA E	
ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 02/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/512,568	HEIN ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *07 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,24-40,43,50,54-63 and 69-100* is/are pending in the application.

4a) Of the above claim(s) *81-100* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,24-40,43,50,54-63 and 69-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 22 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continued Prosecution Application

The request filed on March 1, 2002, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/512568 is acceptable and a CPA has been established. An action on the CPA follows.

The terminal disclaimers filed March 1, 2002, the declaration and amendment filed March 25, 2002, and the amendment filed June 28, 2002, have been entered.

Claims 22, 23, 42, 44-49, 51-53 and 64-68 have been cancelled.

Claims 21, 31-37, 43, 50 and 54-60 are newly amended.

Claims 69-100 are newly added.

Claims 21, 24-40, 43, 50, 54-63 and 69-100 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Election/Restrictions

Applicant's election with traverse of Group I, claims 21, 24-40, 43, 50, 54-63 and 69-80, drawn to plant cells, in Paper No. 24 is acknowledged. The traversal is on the ground(s) that a search and examination of both groups would not be unduly burdensome as the application claims priority to prior cases directed to the same art. This is not found persuasive because the two groups of invention are directed to different types of products that require separate searches. Accordingly, claims 81-100 are withdrawn from consideration as being directed to a nonelected invention.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, filed June 28, 2002, Paper No. 22, is attached to the instant Office action.

Specification

Applicant is required to update the status (pending, allowed, etc.) of all parent priority applications in the specification. The update submitted in the amendment filed March 25, 2002 was not entered because a marked-up version of the update paragraph was not included in the amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 69 and 80, and claims 24-40, 78 and 80 dependent thereon, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Newly amended claim 21 is indefinite in the recitation of "(a)", as "(a)" implies that the claim is composed of more than one subpart. Although previous versions of claim 21 recited subparts (a) and (b), the most recently submitted amendment of claim 21 (submitted June 28, 2002) recites only subpart (a).

Newly added claim 69 is indefinite in the recitation of "wherein the immunoglobulin heavy chain is selected from the group consisting of IgA, IgD, IgE, IgG and IgM", as "IgA, IgD, IgE, IgG and IgM" designate fully assembled multimeric antibodies comprising both light and heavy chains.

Newly added claim 80 is indefinite in the recitation of "derived", as it is unclear what would be retained by the plant of claim 21 from which the plant cell is "derived", and it is unclear what aspects of the plant of claim 21 would be possessed by a cell "derived" from it. It is suggested that the claim be amended to recite "obtained" rather than "derived".

Claim Rejections - 35 USC § 102

The rejection of claims 21, 24-26, 29-39, 43 and 54-61 under 35 U.S.C. 102(b) as being anticipated by During (Dissertation, July 9, 1988, University of Koln, FRG, English translation), is hereby maintained and is further applied to new claims 69, 71, 73, 76-77 and 79-80 for the reasons of record set forth in the office action mailed August 28, 2001.

Newly added claims 69, 71, 73, 76-77 and 79-80 are drawn to plants and plant cells, including tobacco, containing nucleotide sequences encoding an antigen-specific immunoglobulin wherein the immunoglobulin heavy chain is selected from the group consisting of an IgA heavy chain, an IgD heavy chain, an IgE heavy chain, an IgG heavy chain and an IgM heavy chain, and wherein the leader sequence is a plant leader sequence or a non-native leader sequence.

During teaches tobacco plants and cells containing nucleotide sequences encoding an antigen-specific immunoglobulin wherein the immunoglobulin heavy chain is an IgM heavy chain (page 23, page 89, page 112). The barley plant leader sequence taught by During is also non-native to tobacco cells.

Applicant's arguments filed March 25, 2002, have been fully considered but they are not persuasive.

Applicant points to the 1.132 declaration by Richard Lerner submitted to support the argument that During does not anticipate the claimed invention. Applicant argues that the claims are not anticipated because During does not disclose the claim requirements of a leader sequence for each polypeptide that forms a secretion signal which is cleaved, or the assembly of the polypeptides in the plant cell resulting in the formation of a biologically active multimer (reply page 8). Applicant also argues that During's insertion of additional amino acids in the vicinity of the leader cleavage site has the potential to adversely influence proteolytic processing of the leader sequence (reply page 9). Applicant further argues that there was a prejudice in the art against the possibility that plant cells could be used to produce an antigen specific immunoglobulin, and a prejudice in the art against the possibility of using plant cells to process and assemble an antigen specific immunoglobulin, due to the complexity of the native process as it occurs in B cells (reply pages 10-11). Applicant also argues that During's experimental results are internally consistent and lack critical controls. Applicant points to the specific examples of During's failure to detect the production of light chain alone in plants cells transformed with a nucleotide sequence encoding only a light chain, and During's difficulty in detecting assembled antibodies in plants cells transformed with a nucleotide sequence encoding both light and heavy chains. Applicant argues that one skilled the art would not have believed During's assertion that plant cells could be used to produce and assemble an antigen-specific immunoglobulin, and points out that During's publication of his work in a peer-reviewed journal occurred only after publication of Applicant's results (reply pages 11-15).

Regarding the argument that During does not disclose the claim requirement of a leader sequence for each polypeptide that forms a secretion signal which is cleaved, and that During's insertion of additional amino acids in the vicinity of the leader cleavage site has the potential to adversely influence proteolytic processing of the leader sequence the Office notes that the During dissertation teaches an α-amylase leader sequence (page 61) and detection of processed light chain (page 89). Furthermore, that During's insertion of additional amino acids in the vicinity of the leader cleavage site could adversely influence proteolytic processing of the leader sequence is not germane in the absence of evidence that the insertion would have prevented processing. Regarding the argument that During does not disclose the claim requirement of the assembly of the polypeptides in the plant cell resulting in the formation of a biologically active multimer, the Office notes that the rejected claims recite no such requirement. Claim 21 currently requires only that the plant cells contain nucleotide sequences encoding a biologically functional multimeric protein, and claim 23 currently requires only that the plant cells contain nucleotide sequences encoding an antigen-specific immunoglobulin. Regarding the argument that there was a prejudice in the art against the possibility that plant cells could be used to produce an antigen-specific immunoglobulin, this argument is not commensurate in scope with the claims, as the rejected claims are not directed to the production of antigen-specific immunoglobulins in plant cells. Regarding the argument that During's experimental results are internally consistent and lack critical controls, that During required extremely sensitive assays to detect the presence of antibodies or did not include certain controls is not commensurate in scope with the rejected claims, as the rejected claims require only that the plant cells contain nucleotide sequences encoding a biologically functional multimeric protein or encoding an antigen-specific

immunoglobulin. Furthermore, that During required extremely sensitive assays to detect the presence of antibodies or did not include certain controls is also not germane absent evidence that During's assays could not have detected expressed antibodies. Additionally, the publication of During's work in a peer-reviewed journal after the publication of Applicant's results is evidence that weighs in support of the enablement of During.

The rejection of claims 21, 24-27, 29-40, 43 and 54-62 under 35 U.S.C. 102(e) as being anticipated by Goodman (US Pat. No. 4956282), is hereby maintained and is further applied to newly added claims 69-72 , 76-77 and 79-80, for the reasons of record set forth in the office action mailed August 28, 2001.

Newly added claims 69-72 , 76-77 and 79-80 are drawn to plants and plant cells, including tobacco, containing nucleotide sequences encoding an antigen-specific immunoglobulin wherein the immunoglobulin heavy chain is selected from the group consisting of an IgA heavy chain, an IgD heavy chain, an IgE heavy chain, an IgG heavy chain and an IgM heavy chain, and wherein the leader sequence is a plant leader sequence.

While Goodman does not explicitly mention heavy chains obtained from IgA, IgD, IgE, IgG and IgM antibodies, Goodman anticipates the claimed invention as the art classified antibodies as IgA, IgD, IgE, IgG and IgM prior to Goodman's invention, such that the antibodies and heavy chains disclosed by Goodman would necessarily have included heavy chains obtained from IgA, IgD, IgE, IgG and IgM antibodies. Goodman also teaches the use of plant leader sequences (column 3 lines 50-52), as well as tobacco plants (column 8 lines 46-63).

Applicant's arguments filed March 25, 2002, have been fully considered but they are not persuasive.

Applicant argues that Goodman's teachings are limited to the production of gamma interferon in plant cells, which is not a multimer and which is functionally distinct from an immunoglobulin. Applicant also argues that Goodman teaches nothing about immunoglobulin expression in plants, and is not enabling because it does not address any of the factors that one should consider when attempting to obtain assembly of a functional multimeric protein (reply pages 15-16).

Regarding the argument that Goodman's teachings are limited to the production of gamma interferon in plant cells, which is not a multimer and which is functionally distinct from an immunoglobulin, the Office maintains that Goodman teaches the transformation of monocots and dicots by introducing nucleotide sequences encoding interferon (a homomultimer), as well as enzymes and immunoglobulin heavy and light chains (heteromultimers) (column 3 lines 20-30). Furthermore, the rejected claims are not limited to immunoglobulin multimers exclusively. Regarding the argument that Goodman is not enabling because it does not address any of the factors that one should consider when attempting to obtain assembly of a functional multimeric protein, the Office notes that the rejected claims do not require the assembly or presence of a functional multimeric protein in the plant cells, nor do they recite the function that the assembled multimeric proteins would exhibit.

Claim Rejections - 35 USC § 103

The rejection of claims 21, 24-40, 43, 50 and 54-63 under 35 U.S.C. 103(a) as being unpatentable over During (Dissertation, July 9, 1988, University of Koln, FRG, English

translation), as applied to claims 21, 24-26, 29-39, 43 and 54-61 above, and in further view of Applicant's admitted prior art, is hereby maintained and is further applied to new claims 69-80, for the reasons of record set forth in the office action mailed August 28, 2001.

Newly added claims 69-80 are drawn to plants and plant cells, including algae and tobacco, containing nucleotide sequences encoding an antigen-specific immunoglobulin wherein the immunoglobulin heavy chain is selected from the group consisting of an IgA heavy chain, an IgD heavy chain, an IgE heavy chain, an IgG heavy chain and an IgM heavy chain, and wherein the leader sequence is a plant leader sequence or a non-native leader sequence, including sequences from immunoglobulins or yeast.

During's teachings with respect to newly added claims 69, 71, 73, 76-77 and 79-80 are discussed *supra*. While During does not teach the transformation of algae or the use of non-native leader sequences from immunoglobulins or yeast, such methods were known in the art at the time of Applicant's invention and their use in the context of the claimed invention would have been an obvious modification of experimental design parameters.

Applicant's arguments filed March 25, 2002, have been fully considered but they are not persuasive.

Applicant argues that the claims are not anticipated because During does not disclose the claim requirements of a leader sequence for each polypeptide that forms a secretion signal which is cleaved, or the assembly of the polypeptides in the plant cell resulting in the formation of a biologically active multimer (reply page 18). Applicant additionally argues that the claims are not anticipated because During's results would not have been believed by one skilled in the art, and because During is not enabled. Applicant argues that prejudice existed in the art against

the production of antigen-specific immunoglobulins in plant cells During's publication of his work in a peer-reviewed journal occurred after publication by Applicants (reply pages 18-19).

Regarding the argument that During does not disclose the claim requirement of a leader sequence for each polypeptide that forms a secretion signal which is cleaved, and that During's insertion of additional amino acids in the vicinity of the leader cleavage site has the potential to adversely influence proteolytic processing of the leader sequence the Office notes that the During dissertation teaches an α-amylase leader sequence (page 61) and detection of processed light chain (page 89). Furthermore, that During's insertion of additional amino acids in the vicinity of the leader cleavage site could adversely influence proteolytic processing of the leader sequence is not germane in the absence of evidence that the insertion would have prevented processing. Regarding the argument that During does not disclose the claim requirement of the assembly of the polypeptides in the plant cell resulting in the formation of a biologically active multimer, the Office notes that the rejected claims recite no such requirement. Regarding the argument that there was a prejudice in the art against the possibility that plant cells could be used to produce an antigen-specific immunoglobulin, this argument is not commensurate in scope with the claims, as the rejected claims are not directed to the production of antigen-specific immunoglobulins in plant cells. Regarding the argument that During's experimental results are internally consistent and lack critical controls, that During required extremely sensitive assays to detect the presence of antibodies or did not include certain controls is not commensurate in scope with the rejected claims, as the rejected claims require only that the plant cells contain nucleotide sequences encoding a biologically functional multimeric protein or encoding an antigen-specific immunoglobulin. Furthermore, that During required extremely sensitive assays to detect the

presence of antibodies or did not include certain controls is also not germane absent evidence that During's assays could not have detected expressed antibodies. Additionally, the publication of During's work in a peer-reviewed journal after the publication of Applicant's results is evidence that weighs in support of the enablement of During.

The rejection of claims 21, 24-40, and 43, 50, 54-63 under 35 U.S.C. 103(a) as being unpatentable over Goodman (US Pat. No. 4956282), as applied to claims 21, 24-27, 29-40, 43 and 54-62 above, and in further view of Applicant's admitted prior art, is hereby maintained and is further applied to new claims 69-80, for the reasons of record set forth in the office action mailed August 28, 2001.

Newly added claims 69-80 are drawn to plants and plant cells, including algae and tobacco, containing nucleotide sequences encoding an antigen-specific immunoglobulin wherein the immunoglobulin heavy chain is selected from the group consisting of an IgA heavy chain, an IgD heavy chain, an IgE heavy chain, an IgG heavy chain and an IgM heavy chain, and wherein the leader sequence is a plant leader sequence or a non-native leader sequence.

Goodman's teachings with respect to newly added claims 69-72, 76-77 and 79-80 are discussed *supra*. While Goodman does not teach the transformation of algae or the use of non-native leader sequences, such methods were known in the art at the time of Applicant's invention and their use in the context of the claimed invention would have been an obvious modification of experimental design parameters.

Applicant's arguments filed March 25, 2002, have been fully considered but they are not persuasive.

Applicant argues that Goodman's teachings are limited to the production of gamma interferon in plant cells, which is not a multimer and which is functionally distinct from an immunoglobulin. Applicant also argues that Goodman teaches nothing about immunoglobulin expression in plants, and is not enabling because it does not address any of the factors that one should consider when attempting to obtain assembly of a functional multimeric protein (reply pages 19-20).

Regarding the argument that Goodman's teachings are limited to the production of gamma interferon in plant cells, which is not a multimer and which is functionally distinct from an immunoglobulin, the Office maintains that Goodman teaches the transformation of monocots and dicots by introducing nucleotide sequences encoding interferon (a homomultimer), as well as enzymes and immunoglobulin heavy and light chains (heteromultimers) (column 3 lines 20-30). Furthermore, the rejected claims are not limited to immunoglobulin multimers exclusively. Regarding the argument that Goodman is not enabling because it does not address any of the factors that one should consider when attempting to obtain assembly of a functional multimeric protein, the Office notes that the rejected claims do not require the assembly or presence of a functional multimeric protein in the plant cells, nor do they recite the function that the assembled multimeric proteins would exhibit.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (703) 605-1210. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

CC
February 4, 2003

Phuong Bui

PHUONG T. BUI
PRIMARY EXAMINER

2/8/03